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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/033,244	12/27/2001	David Botstein	P2930R1C2	1015

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EXAMINER
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FREDMAN, JEFFREY NORMAN

ART UNIT	PAPER NUMBER
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1634

DATE MAILED: 10/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

10/033,244

Applicant(s)

BOTSTEIN ET AL.

Examiner

Jeffrey Fredman

Art Unit

1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 06 August 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 22-27 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 22-27 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_ 6) ☐ Other: \_\_\_\_\_

## DETAILED ACTION

### *Priority*

Priority is granted to PCT 99/28634, published as WO 00/36102, since that application has the claimed protein sequence in figure 2.

### ***Claim Rejections - 35 USC § 101***

1. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

2. Claims 22-27 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility.

The current claims are drawn to a genus of antibodies which bind to a protein termed PRO1800 in the specification.

### **Credible Utility**

Following the requirements of the Utility Guidelines (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for Utility.), the first inquiry is whether a credible utility is cited in the specification for use of the proteins. The cited utilities in the specification are that the protein is related to the Hep27 protein, which the specification states may be involved in some DNA synthesis related pathway. There is some evidence of overexpression in certain lung tumors (but not in others) at page 117. These utilities are credible.

Upon identification of credible utilities, the next issue is whether there are any well established utilities for the protein. No well established utilities for this specific

PRO1800 protein, antibody or nucleic acid are identified in either the specification or in the cited prior art.

**Substantial utility**

Given the absence of a well established utility, the next issue is whether substantial utilities are disclosed in the specification. Here, the evidence in the specification provided is that the protein is related by homology to the Hep 27 protein. This relationship lacks any of the hallmarks of utility. The homology does not imply that the proteins are similar in any function way, or that they are expressed in similar tissue types or under similar conditions. There is no biological activity, expression pattern, phenotype, disease or condition, ligand, binding partner or any other specific feature which is disclosed as being associated with PRO1800. Without any further information, there is no expectation that the protein will have any properties in common with the Hep 27 protein. There is an abundance of evidence that very similar proteins can perform very different functions. For example, Rost et al (J. Mol. Biol. (2002) 318(2):595-608) notes regarding assignment of enzymatic activity based upon homology comparisons that "The results illustrated how difficult it is to assess the conservation of protein function and to guarantee error-free genome annotations, in general: sets with millions of pair comparisons might not suffice to arrive at statistically significant conclusions (abstract)." Thus, even high levels of homology do not necessarily correlate with actual protein function. In the current case, where not only is the function of PRO1800 not known, but no specific function has been definitively identified for the related Hep 27

protein itself, the expectation is even lower that there is any utility that can be derived based upon this association.

As noted in the utility guidelines, basic research on a product to identify properties and intermediate products which themselves lack substantial utility are all insubstantial utilities (see page 6 of the Utility guideline training materials). First, there is NO data in the specification showing association of PRO1800 with any disease state.

Second, the overexpression data does not provide a substantial utility for several reasons. First, there is no showing that the overexpression was statistically significant and correlated with any diagnostic utility. The absence of such a diagnostic utility is particularly striking since there is no evidence that the overexpression effect was statistically significant, that the effect was reproducible, or that the effect was anything other than a nonspecific effect due to the presence of an exogenous protein in the mixture.

### **Specific Utility**

In the current case, even if the substantial utility argument above were found unpersuasive, there is no specific utility given for this protein and resultant nucleic acid. The protein has not been associated with any disease, any condition, any enzymatic activity or any other specific feature. The only association is that it has some homology to a protein, Hep 27, which is associated with DNA synthesis in some undefined way. As the utility guideline training materials note on page 5-6, "Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would

ordinarily be insufficient absent a disclosure of what condition can be diagnosed". Here, there is no disclosure of any condition which can be diagnosed and hence, no specific utility.

Finally, with regard to the utility analysis, the current situation directly tracks Example 4 of the utility guidelines, where a protein of entirely unknown function was characterized as lacking utility.

***Claim Rejections - 35 USC § 112 – Scope of Enablement***

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 22-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state

of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.”

The nature of the invention

The claims are drawn to antibodies which bind the PRO1800 protein. The invention is in a class of invention which the CAFC has characterized as “the unpredictable arts such as chemistry and biology.” *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims broadly encompass any antibody which binds to the PRO1800 protein and also include any antibody fragments which bind to the PRO1800 protein.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant variability in the activity of polypeptides and antibodies. It would require significant study to identify the actual function of the PRO1800 protein, and identifying a use for this protein would be an inventive, unpredictable and difficult undertaking in itself. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

The unpredictability of the art and the state of the prior art

The art is extremely unpredictable with regard to protein function in the absence of reliable information regarding the protein activity. Even very similar proteins, as shown by homology, may have very different functions (see Rost et al (J. Mol. Biol.

(2002) 318(2):595-608). In the current case, where no specific information is known regarding the function of the protein in actual biological organisms, it is entirely unpredictable what function and activity will be found for this protein. The prior art does not resolve this ambiguity, since no prior art activity is identified for the protein.

#### Working Examples

The specification has one working example in which the nucleic acid may be overexpressed in some tumor samples, but the working example lacks sufficient information regarding internal controls to show that the protein was, in fact, overexpressed, that the nucleic acid was associated with any disease or that the results are anything other than spurious.

#### Guidance in the Specification.

The specification, while correlating PRO1800 with Hep 27, did not teach any actual function or use for PRO1800, nor, in fact, any use for Hep 27 itself.

#### Level of Skill in the Art

The level of skill in the art is deemed to be high.

#### Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of a working example which does not address the issue of the efficacy of the control and the negative teachings in the prior art balanced only against the high skill level in the art,



it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

***Claim Rejections - 35 USC § 102***

5. The 102 rejection is withdrawn in view of the granting of Applicant's priority date. While Applicant's other arguments were not persuasive and would not have led to the withdrawal of the rejection, the priority argument is persuasive since Bandman is no longer prior art, and cannot be applied under 35 U.S.C. 102 or 103.

***Response to Arguments***

6. Applicant's arguments filed August 6, 2003 have been fully considered but they are not persuasive.

Applicant argues that the claims, drawn here to antibodies, have utility because the nucleic acid is overexpressed in certain cancerous cells. Applicant supports this argument by citation to a declaration, of Dr. Goddard, which argues that a 2 fold overexpression of the nucleic acid is useful in the diagnosis of cancer. The declaration is not persuasive on the central issue of utility in this case. The argument regarding nucleic acid overexpression, which was found persuasive in a related case in which a nucleic acid was claimed, is not relevant to the current case where the claims are drawn to antibodies. The fact that the nucleic acid can be used in diagnosis of cancer does not provide any utility for the polypeptide encoded by that nucleic acid or the antibodies which interact with that polypeptide. There is no real world use for the antibody simply because the nucleic acid is overexpressed in certain cancerous cell lines. The

antibody, of course, cannot be used to detect the overexpression of the nucleic acid, since antibodies bind to proteins.

Applicant argues that the protein has utility in tissue typing. There is no evidence that the protein is expressed in any particular tissue type. There is no evidence that the protein is overexpressed in cancerous cells, or that the protein has any utility whatsoever. As numerous references show, there is no necessary relationship between nucleic acid expression in a cell and protein expression. For example, Pennica et al (Proc. Natl. Acad. Sci. (1998) 95:14717-14722) shows that the Wisp-2 DNA was amplified by the RNA expression was reduced in tumors (see abstract). Konopka (Proc. Natl. Acad. Sci. (1986) 83:4049-4052) states that "Protein expression is not related to amplification of the abl gene but to variation in the level of bcr-abl mRNA produced from a single Ph1 template. (see abstract)." So the fact that there is a gene amplification provides no utility whatsoever for the protein or antibody, since they do not necessarily provide information regard the cancerous state.

The same argument above applies to the enablement rejection, since there is no known use for the antibody, the antibody is not enabled for any use.

### ***Conclusion***

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).


A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.



Jeffrey Fredman  
Primary Examiner  
Art Unit 1634

September 26, 2003